PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
10242-20		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/00250	25/03/1999	26/03/1998
Applicant		
UNIVERSITY OF SASKATCHEWAN TECHNOLOGIES INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/CA 99/ 00250

Box I Observations where certain claims w re f und un archable (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.Claims: 1-25 (all part) Compounds according to formula (I) wherein n = 1
2.Claims: 1-25 (all part) Compounds according to formula (I) wherein n = 2
3.Claims: 1-25 (all part) Compounds according to formula (I) wherein n = 3

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 to 6, 10 to 17, 20 to 25, 26 (all in part)

Claim 1 is unclear, since the subject-matter of claim 1, which includes the subject-matter of the dependent claim 5, does not contain the disclaimers of claim 5. Therefore all the compounds disclaimed in claim 5 are novelty destroying for the subject-matter of claim 1 as well as for the claims 2 to 4 and 6.
It is stressed that the scope of claim 6 is broader than the scope of claim 1, because the substituent R1 could be substituted.
Claim 5 contains so many provisos that a lack of clarity and concisness within the meaning of Art. 6 PCT arises to such extent as to render a meaningful search of the claims impossible.
The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to dertermine which parts of the claims (claims 1-4 and 6 for instance) may be said to define subject-matter for which protection might legitimately be sought (Art. 6 PCT).
For all these reasons, a meaningful search over the hole breadth of the claims is impossible. Consequently, the search has been restricted to claims 7, 8, 9, 18, 19, 23.

Claim 26 discloses a commercial package, which is defined by the use of the pharmaceutical composition contained in it and not by features of the package itself.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

[redacted] national Application No
PCT/CA 99/00250

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/12 C07C255/24 C07C255/25 C07F9/38 C07F9/40
C07D257/04 A61K31/195 A61K31/215 A61K31/275 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07F C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 45115 A (TROPHIX PHARM INC) 4 December 1997 (1997-12-04) page 23 -page 28; claims 1,24 ---	1,6, 10-17, 20-22, 24,25
X	WO 92 15551 A (UNIV SASKATCHEWAN) 17 September 1992 (1992-09-17) claims 1,30 --- -/--	1-5,26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1999	26. NOV. 1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Rufet, J

6

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KUNIKO NISHIMURA ET AL.: "Inactivation of monoamine oxidase B by analogues of the anticonvulsant agent milacemide (2-(n-pentylamino)acetamide)" JOURNAL OF MEDICINAL CHEMISTRY., vol. 36, no. 4, 1993, pages 446-448, XP002109875 WASHINGTON US page 447, column 2 -page 448, column 1	1-7,9
X	DE 41 00 856 A (KOREA INST SCIENCE TECHNOLOGY) 2 October 1991 (1991-10-02) examples 1-6	1-6
X	DE 11 39 738 B (GENERAL ANILINE & FILM CORPORATION) 15 November 1962 (1962-11-15) page 14; table II	1-6
X	DE 20 52 256 A (CILAG CHEMIE AG) 6 May 1971 (1971-05-06) page 23; example 29	1-6
X	DE 24 42 239 A (SUMITOMO CHEMICAL CO) 13 March 1975 (1975-03-13) * page 2, compound 8 *	1-6
X	DE 25 55 769 A (BASF AG) 16 June 1977 (1977-06-16) example 5	1-6
X	DE 15 67 221 A (VEB BERLIN-CHEMIE) 16 April 1970 (1970-04-16) page 2 -page 4	1-6
A	WO 96 05286 A (FRONTIER KK) 22 February 1996 (1996-02-22) abstract	1,20-25
X	CHEMICAL ABSTRACTS, vol. 55, no. 15, 1961 Columbus, Ohio, US; abstract no. 14441b, GERHARD SATZINGER: "5-Substituted and 1,5-condensed tetrazoles." page 14441; column 1; XP002109056 abstract & ANN., vol. 638, 1960, pages 159-173,	1-6

-/--

6

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FREDERICK LEONARD ET AL.: "Potential antiviral agents." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 78, no. 6, 20 March 1956 (1956-03-20), pages 1199-1201, XP002109053 DC US page 1199; table I ---	1-6
X	HANS-G. BOIT: "BEILSTEINS HANDBUCH DER ORGANISCHEN CHEMIE, 4. Edition, 3. suppl., vol. 4, part 2" 1963 , SPRINGER-VERLAG XP002109054 page 1137, paragraph 9 ---	1-6
X	REINER LUCKENBACH: "BEILSTEINS HANDBUCH DER ORGANISCHEN CHEMIE, 4. Edition, 4. suppl., vol. 4, part 3" 1980 , SPRINGER-VERLAG XP002109055 page 2386, paragraph 3 ---	1-6
X	SHIGEYOSHI MIYAGISHI ET AL.: "Phase transition of N-acyl amino acids with different acyl group" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN., vol. 59, no. 2, 1986, pages 557-562, XP002109876 JAPAN PUBLICATIONS TRADING CO. TOKYO., JP ISSN: 0009-2673 page 557; table 1 ---	1-6
X	FR 2 451 913 A (CONTINENTAL PHARMA) 17 October 1980 (1980-10-17) claims 1,15; example 5 ---	1-6,9-12
X	CHEMICAL ABSTRACTS, vol. 92, no. 23, 1980 Columbus, Ohio, US; abstract no. 192462w, KIRINO, OSAMU ET AL.: "Studies on anti-fusarium disease activity of aminonitrile derivatives....." page 167; column 2; XP002122173 abstract & AGRIC. BIOL. CHEM. , vol. 44, no. 1, 1980, pages 31-34, --- -/--	1-6,9-12

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JOSEPH CORSE ET AL.: "N-substituted 2-methoxy-6-chloro-9-aminoacridines derived from unsymmetrical aliphatic amines" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 68, 1946, pages 1905-1910, XP002122172 DC US table II ---	1-6,9
X	CHEMICAL ABSTRACTS, vol. 74, no. 8, 1971 Columbus, Ohio, US; abstract no. 32910r, ISHIZUKA, TETSUO ET AL.: "Alkyl-beta-amines from long-chain olefins" page 70; column 1; XP002122174 abstract & CHIM. PHYS. APPL. PRAT. AG. SURFACE, C. R. CONGR. INT. DETERG., 5TH, vol. 1, 1968, pages 183-191, ---	1-6
X	CHEMICAL ABSTRACTS, vol. 55, no. 8, 1961 Columbus, Ohio, US; abstract no. 7275d, SEIZABURO SAKAKIBARA ET AL.: "Cationic surface-active agents from long-chain alkyl amines and acrylonitrile" page 7275; column 1; XP002122175 abstract & YUKAGAKU, vol. 6, 1957, pages 263-266, ---	1-6
X	CHEMICAL ABSTRACTS, vol. 55, no. 15, 24 July 1961 (1961-07-24) Columbus, Ohio, US; abstract no. 14441b, GERHARD SATZINGER: "5-substituted and 1,5-condensed tetrazoles." page 14441; column 1; XP002122176 abstract & ANN., vol. 638, 1960, pages 159-173, --- -/--	1-6

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 55, no. 23, 13 November 1961 (1961-11-13) Columbus, Ohio, US; abstract no. 23837e, HISASHI TAKAHASHI: "Effects of derivatives of gamma-aminobutyric acid ...." page 23837; column 1; XP002122177 abstract & NIPPON SEIRIGAKU ZASSHI, vol. 23, 1961, pages 417-425, ---	1-6
X	US 4 548 726 A (MORRIS-SHERWOOD BETTY J ET AL) 22 October 1985 (1985-10-22) abstract ---	1-6
X	US 3 991 208 A (DUDZINSKI ZDZISLAW W ET AL) 9 November 1976 (1976-11-09) abstract -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/00250

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9745115	A	04-12-1997	AU	3153097 A	05-01-1998
			CA	2254833 A	04-12-1997
			NO	985711 A	07-12-1998
WO 9215551	A	17-09-1992	US	5169868 A	08-12-1992
			AT	173459 T	15-12-1998
			AU	658611 B	27-04-1995
			AU	1323692 A	06-10-1992
			CA	2105171 A	02-09-1992
			DE	69227627 D	24-12-1998
			DE	69227627 T	24-06-1999
			EP	0573498 A	15-12-1993
			JP	6505241 T	16-06-1994
			US	5508311 A	16-04-1996
DE 4100856	A	02-10-1991	JP	1877781 C	07-10-1994
			JP	3279390 A	10-12-1991
			JP	6004658 B	19-01-1994
			US	5099056 A	24-03-1992
DE 1139738	B		GB	912266 A	
DE 2052256	A	06-05-1971	AT	302348 B	15-09-1972
			BE	758165 A	28-04-1971
			DK	324975 A	20-10-1975
			ES	384946 A	01-09-1973
			FR	2070171 A	10-09-1971
			GB	1287317 A	31-08-1972
			NL	7015825 A	03-05-1971
			SE	356044 B	14-05-1973
			CH	543487 A	14-12-1973
			DK	131933 B	29-09-1975
			JP	49048548 B	21-12-1974
			JP	50026541 B	01-09-1975
			US	3703537 A	21-11-1972
			US	3755415 A	28-08-1973
			US	3786056 A	15-01-1974
DE 2442239	A	13-03-1975	JP	956306 C	31-05-1979
			JP	50101525 A	12-08-1975
			JP	53033657 B	16-09-1978
			JP	50101526 A	12-08-1975
			JP	946802 C	30-03-1979
			JP	50101530 A	12-08-1975
			JP	53022144 B	06-07-1978
			JP	910778 C	14-06-1978
			JP	50105825 A	20-08-1975
			JP	52041330 B	18-10-1977
			JP	850757 C	19-03-1977
			JP	50049420 A	02-05-1975
			JP	51024569 B	24-07-1976
			AU	475364 B	11-03-1976
			DK	467874 A	05-05-1975
			FR	2242374 A	28-03-1975
			NL	7411789 A	07-03-1975
			AU	7301774 A	11-03-1976
			US	3966789 A	29-06-1976
			ZA	7405500 A	28-04-1976

INTERNATIONAL SEARCH REPORT

ation on patent family members

International Application No
PCT/CA 99/00250

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2555769 A	16-06-1977	BE 848353 A	16-05-1977
		CH 628325 A	26-02-1982
		FR 2334666 A	08-07-1977
		GB 1560549 A	06-02-1980
		US 4113764 A	12-09-1978
DE 1567221 A	16-04-1970	FR 1455235 A	30-12-1966
		GB 1048507 A	
WO 9605286 A	22-02-1996	JP 8056655 A	05-03-1996
		EP 0723583 A	31-07-1996
		US 5792479 A	11-08-1998
FR 2451913 A	17-10-1980	LU 81068 A	08-10-1980
		LU 81069 A	08-10-1980
		AT 381302 B	25-09-1986
		AT 154680 A	15-02-1986
		AT 391134 B	27-08-1990
		AT 275084 A	15-02-1990
		AT 392271 B	25-02-1991
		AT 275184 A	15-08-1990
		AU 536499 B	10-05-1984
		AU 5678480 A	25-09-1980
		CA 1184567 A	26-03-1985
		CH 645091 A	14-09-1984
		DE 3010599 A	09-10-1980
		DE 3050800 C	22-06-1989
		DK 123580 A,B,	23-09-1980
		ES 490536 A	16-04-1981
		FI 800900 A,B,	23-09-1980
		GB 2048852 A,B	17-12-1980
		GR 68005 A	26-10-1981
		IE 49751 B	11-12-1985
		IL 59679 A	30-11-1984
		JP 1462820 C	28-10-1988
		JP 55143944 A	10-11-1980
		JP 63009491 B	29-02-1988
		NL 8001721 A,B,	24-09-1980
		NO 800830 A	23-09-1980
		PT 70992 A	01-04-1980
		SE 453917 B	14-03-1988
		SE 8002204 A	23-09-1980
		US 4639468 A	27-01-1987
		ZA 8001682 A	26-08-1981
US 4548726 A	22-10-1985	NONE	
US 3991208 A	09-11-1976	US 3974208 A	10-08-1976

16

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
10242-20		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00250	25/03/1999	26/03/1998
International Patent Classification (IPC) or national classification and IPC C07C229/12		
Applicant UNIVERSITY OF SASKATCHEWAN TECHNOLOGIES INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **6** sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/10/1999	28.[illegible]
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Grammenoudi, S Telephone No. +49 89 2399 8324

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00250

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-38 as originally filed

Claims, No.:

1-24 as received on 19/06/2000 with letter of 19/06/2000

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they hav been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 17-23,24.

because:

☒ the said international application, or the said claims Nos. 17-23 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separat sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 24 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5-7,13-15,21
	No:	Claims	1-4,8-12,16-20,22-23
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION III

1. Claim 24 discloses a commercial package, which is defined by the use of the pharmaceutical composition contained in it and not by the features of the package itself. Therefore an examination of such a claim cannot be carriet out.

2. Claims 17-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT.

   For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

INVENTION A

The examination is being carried out on the basis of present claims 1-23 wherein n is 1 in formula I.

D2= WO-A-92/15551

1. The present application relates to aliphatic amino derivatives for use as cellular rescue agents.

2. Document D2, which is considered to represent the closest state of the art, discloses aliphatic propargylamines for the treatment of neurodegenerative disorders in mammals such as Alzheimer´s disease, Parkinson´s disease, Huntington´s disease and stroke (see D2, paragraph bridging pages 22 and 23). It is believed that these disorders involve apoptotic processes.

3. The problem to be solved by the present application with respect to D2 is seen in the provision of alternative compounds usable as cellular rescue agents for the treatment and prevention of diseases in which cell death occurs by apoptosis.

4. The compounds of present claims 1-10 differ from the propargyl amines known from D2 in that the group X cannot be alkynyl. These compounds, their use (claims 17-23) as well as compositions (claims 11-16) comprising them, are therefore novel. Some compounds involved in claims 17-23 are known from the prior art but not their use for the claimed purpose. Accordingly, the subject-matter of claims 1-23 meets the requirements of Article 33(2) PCT.

5. The above technical problem can only be regarded as having been solved if, in deciding the issue under Article 33(3) PCT, it would be credible that all compounds within the scope of present claims 1-4 are useful as cellular rescue agents. It is stated, however, in the description on pages 3 and 8 that for a particular class or subclass of the claimed compounds the inactive enantiomer does not prevent apoptosis but can antagonize the antiapoptotic actions of the active enantiomers. Indeed, the biological data according to Example 1 clearly show that a number of individual compounds falling within the scope of present claims 1-4 does not exhibit antiapoptotic properties at all (cf. Tables 1-4) and hence does not solve the problem posed.

   It is also obvious from Tables 1-4 that even minor structure changes can lead to a total loss of antiapoptotic activity. For instance, whereas (R)-2-(2-pentylamino)acetonitrile is active and (R)-2-(2-heptylamino)acetonitrile inactive, (S)-2-(2-pentylamino)acetonitrile is inactive and (S)-2-(2-heptylamino)acetonitrile active (cf. Table 4). Apparently, reliable predictions concerning the influence of stuctural changes and chirality of the claimed compounds on their antiapoptotic properties are not possible.

   It should be also noted that from the vast number of possible meanings for R_1 only some few examples of alkyl groups are presented in the biological examples. Thus, taking into account the broad definition of claims 1-4 as compared to the very narrow structural range of the compounds tested in Example 1 , it is inherently unlikely that all remaining compounds claimed possess the alleged antiapo-

ptotic properties.

The compounds according to claims 1-4, their use for the treatment or prevention of a disease in which cell death occurs by apoptosis as well as the compositions comprising these compounds are therefore regarded as not involving an inventive step. Accordigly, the subject-matter of claims 1-4, 8-12, 16-20 and 22-23 does not satisfy the requirements of Article 33(3) PCT.

6. The antiapoptotic activity of the individual compounds according to the remaining claims is considered to be credible. Claims 5-7, 13-15 and 21 therefore meet the requirements of Article 33(3) PCT.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

SECTION VIII

1. The term "lower" in connection with acyloxy (cf. claims 1, 11 and 17) is unclear since the upper limit to the number of C-atoms is not defined (Art. 6 EPC).

INVENTION B

The examination is being carried out on the basis of present claims 1-23 wherein n is 2 in formula I.

D2= WO-A-92/15551

1. The present application relates to aliphatic amino derivatives for use as cellular rescue agents.

2. Document D2, which is considered to represent the closest state of the art, discloses aliphatic propargylamines for the treatment of neurodegenerative disorders in mammals such as Alzheimer's disease, Parkinson's disease, Huntington's disease and stroke (see D2, paragraph bridging pages 22 and 23). It is believed that these disorders involve apoptotic processes.

3. The problem to be solved by the present application with respect to D2 is seen in the provision of alternative compounds usable as cellular rescue agents for the treatment and prevention of diseases in which cell death occurs by apoptosis.

4. The compounds of present claims 1-10 differ from the propargyl amines known from D2 in that the group X cannot be alkynyl. These compounds, their use (claims 17-23) as well as compositions (claims 11-16) comprising them are therefore novel. Some compounds involved in claims 17-23 are known from the prior art but not their use for the claimed purpose. Accordingly, the subject-matter of claims 1-23 meets the requirements of Article 33(2) PCT.

5. The above technical problem can only be regarded as having been solved if, in deciding the issue under Article 33(3) PCT, it would be credible that all compounds within the scope of present claims 1-4 are useful as cellular rescue agents. It is stated, however, in the description on pages 3 and 8 that for a particular class or subclass of the claimed compounds the inactive enantiomer does not prevent apoptosis but can antagonize the antiapoptotic actions of the active enantiomers. Indeed, the biological data according to Example 1 clearly show that a number of individual compounds falling within the scope of present claims 1-4 does not exhibit antiapoptotic properties at all (cf. Tables 1-4) and hence does not solve the problem posed.

   It is also obvious from Tables 1-4 that even minor structure changes can lead to a total loss of antiapoptotic activity. For instance, while (R)-3-(2-heptylamino)propionic acid is active as a cellular rescue agent, the 2-pentyl homologue is not (cf. Table 1). In striking contrast to this, R-2-(2-pentylamino)ethane phosphonic acid is active (cf. Table 2). Apparently, reliable predictions concerning the influence of structural changes and chirality of the claimed compounds on their antiapoptotic properties are not possible.

It should be also noted that from the vast number of possible meanings for R_1 only some few examples of alkyl groups are presented in the biological examples. Thus, taking into account the broad definition of claims 1-4 as compared to the very narrow structural range of the compounds tested in Example 1 , it is inherently unlikely that all remaining compounds claimed possess the alleged antiapoptotic properties.

The compounds according to claims 1-4, their use for the treatment or prevention of a disease in which cell death occurs by apoptosis as well as the compositions comprising these compounds are therefore regarded as not involving an inventive step. Accordigly, the subject-matter of claims 1-4, 8-12, 16-20 and 22-23 do not satisfy the requirements of Article 33(3) PCT.

6. The antiapoptotic activity of the individual compounds according to the remaining claims is considered to be credible. Claims 5-7, 13-15 and 21 therefore meet the requirements of Article 33(3) PCT.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

SECTION VIII

1. The term "lower" in connection with acyloxy (cf. claims 1, 11 and 17) is unclear since the upper limit to the number of C-atoms is not defined (Art. 6 EPC).

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 November 1999 (22.11.99)	
International application No. PCT/CA99/00250	**Applicant's or agent's file reference** 10242-20
International filing date (day/month/year) 25 March 1999 (25.03.99)	**Priority date** (day/month/year) 26 March 1998 (26.03.98)
Applicant DYCK, Lilian, E. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 October 1999 (14.10.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 229/00 | A2

(11) International Publication Number: **WO 99/48858**

(43) International Publication Date: 30 September 1999 (30.09.99)

(21) International Application Number: PCT/CA99/00250

(22) International Filing Date: 25 March 1999 (25.03.99)

(30) Priority Data:
60/079,488 26 March 1998 (26.03.98) US
60/079,489 26 March 1998 (26.03.98) US

(71) Applicant *(for all designated States except US)*: UNIVERSITY OF SASKATCHEWAN TECHNOLOGIES INC. [CA/CA]; 117 Science Place, Saskatoon, Saskatchewan S7N 5C8 (CA).

(71) Applicant *(for US only)*: THE CANADA TRUST COMPANY (executor for the deceased inventor) [CA/CA]; Suite 800, 421 7th Avenue, Calgary, Alberta T2P 3Y8 (CA).

(72) Inventor: PATERSON, I., Alick (deceased).

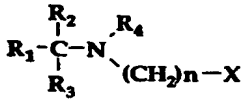
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DYCK, Lilian, E. [CA/CA]; 1140 Temperance Street, Saskatoon, Saskatchewan S7N 0N8 (CA). DAVIS, Bruce, A. [CA/CA]; 819 Coppermine Crescent, Saskatoon, Saskatchewan S7K 4K9 (CA). LIU, Ya-Dong [CA/CA]; #1 – 1308 Temperance Street, Sakatoon, Saskatchewan S7N 0P5 (CA). DURDEN, David, A. [CA/CA]; 55 Kirk Crescent, Saskatoon, Saskatchewan S7H 5B1 (CA). BOULTON, Alan, A. [CA/CA]; 306–921 Main Street, Saskatoon, Saskatchewan S7H 0K4 (CA).

(74) Agent: BERESKIN & PARR; 40th floor, 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: ALIPHATIC AMINO CARBOXYLIC AND AMINO PHOSPHONIC ACIDS, AMINO NITRILES AND AMINO TETRAZOLES AS CELLULAR RESCUE AGENTS



(I)

(57) Abstract

Novel compounds of formula (I) are described wherein: $R_1=(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms; R_2=H, CH_3 or CH_2CH_3; R_3=H or CH_3; R_4=H or CH_3; R_5= lower alkyl having from 1 to 5 carbon atoms; n is an integer in the range from 1 to 3, and X is carboxyl (COOH) or carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5–tetrazole, and pharmaceutically acceptable salts thereof. Preferably, the compounds are optically pure enantiomers of the R– or S–configuration in which $R_3=R_4=R_5$=H, $R_2=CH_3$ and R_1 is a saturated aliphatic chain of one to five carbon atoms. The compounds are useful as cellular rescue agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Title: ALIPHATIC AMINO CARBOXYLIC AND AMINO PHOSPHONIC ACIDS, AMINO NITRILES AND AMINO TETRAZOLES AS CELLULAR RESCUE AGENTS

FIELD OF THE INVENTION

The invention relates to novel aliphatic amino carboxylic and amino phosphonic acids, amino nitriles and amino tetrazoles, their salts, compositions containing such compounds and to the use of such compounds as cellular rescue agents in human and veterinary medicine.

BACKGROUND OF THE INVENTION

Neurodegenerative disorders (for example, chronic disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Picks's disease, amyotrophic lateral sclerosis and glaucoma as well as acute injuries like stroke, head trauma, Bell's palsy and spinal cord injuries) are now believed to involve apoptotic processes.

Deprenyl, the aliphatic propargylamines, their respective desmethyl analogues and rasagiline have been shown to protect and rescue damaged neurons in several models of degeneration [1-16]. The propargyl group was thought to be a requirement for the protective or rescuing activity of these drugs. Previous studies have examined the N-demethylation and/or depropargylation of these drugs [7, 17].

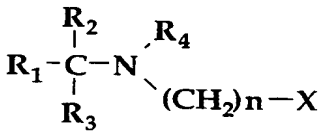
It has been known for some time that some aliphatic and aromatic acetylenic compounds react with P450 enzymes. One of these reactions results in oxidation of the terminal carbon of the acetylenic functional group to form the corresponding acid [18-20]. The possibility of oxidation of the N-acetylene group of the aliphatic propargylamines to form carboxylic acid metabolites has not been previously addressed. The potential of related acidic compounds (the amino phosphonic acids and amino tetrazoles) and precursors to such compounds (amino nitriles and amino esters) as antiapoptotic agents had also not been previously considered.

The present inventors have found that aliphatic amino carboxylic and amino phosphonic acids, amino nitriles and amino

tetrazoles are antiapoptotic agents and may be useful as cellular rescue agents in human and animal treatments.

SUMMARY OF THE INVENTION

The present invention relates to a compound of the general formula (I),



Formula (I)

wherein:

R_1 is $(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms. R_1 may be unsubstituted or substituted with at least one of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3 and 6 atoms, of which from 1 to 3 are heteroatoms selected from O, S and/or N,

R_2 = H, CH_3 or CH_2CH_3,

R_3 = H or CH_3,

R_4 = H or CH_3,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, and the salts thereof, particularly pharmaceutically acceptable salts thereof.

Compounds of the general formula I in which R_1, R_2 and R_3 differ from one another are chiral. It has been found that the R-enantiomers of some of these classes or sub-classes of compounds (and the S-enantiomers for other classes or subclasses) are useful as cellular

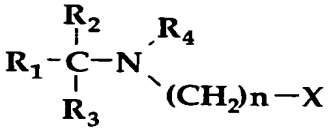
rescue agents for the treatment and prevention of diseases in which cell death occurs by apoptosis, such as in many neurodegenerative disorders. For a particular class or subclass of compounds the inactive enantiomer does not prevent apoptosis but can antagonize the antiapoptotic actions of the active enantiomers, and are useful as research tools. The achiral compounds also display cellular rescue properties.

The present invention also relates to the use of compounds of general formula I, as defined above, and salts thereof, as cellular rescue agents for the treatment and prevention of diseases in which cell death occurs by apoptosis including but not limited to, stroke, head trauma, Bell's palsy, spinal cord and other nerve crush injuries, Alzheimer's disease, Parkinson's disease, Pick's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, cardiac myopathies, nephropathy, retinopathy, diabetic complications, glaucoma, as well as idiopathic neuropathies. Accordingly, the present invention provides a method for treating a condition wherein cell death occurs by apoptosis comprising administering an effective amount of a compound of the formula I to an animal in need thereof.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Compounds of the Invention

The present invention relates to compounds of the general formula I,



Formula (I)

wherein:

R_1 is $(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms. R_1 may be unsubstituted or substituted with at least one

of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3 and 6 atoms, of which from 1 to 3 are heteroatoms selected from O, S and/or N,

R_2 = H, CH_3 or CH_2CH_3,

R_3 = H or CH_3,

R_4 = H or CH_3,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, and the salts thereof.

In a preferred embodiment, the present invention provides a compound of the Formula I (as described above) wherein

$R_1 = (CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16,

$R_2 = CH_3$,

R_3 = H,

R_4 = H or CH_3,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH) or carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

Preferred compounds of the invention include:

2-(2-Propylamino)acetic acid;

2-(1-Hexylamino)acetic acid;

(S)-2-(2-Heptylamino)acetic acid;

3-(2-Propylamino)propionic acid;

3-(1-Hexylamino)propionic acid;

(R)-3-(2-Heptylamino)propionic acid;

2-(2-Propylmethylamino)acetic acid;

2-(1-Hexylmethylamino)acetic acid;

(S)-2-(2-Heptylmethylamino)acetic acid;

3-(2-Propylmethylamino)propionic acid;

3-(1-Hexylmethylamino)propionic acid;

(R)-3-(2-Heptylmethylamino)propionic acid;

2-(2-Propylamino)acetonitrile;

(R)-2-(2-Pentylamino)acetonitrile;

2-(1-Hexylamino)acetonitrile;

(S)-2-(2-Heptylamino)acetonitrile;

(R)-3-(2-Heptylamino)propionitrile;

2-(2-Propylmethylamino)acetonitrile;

(R)-2-(2-Pentylmethylamino)acetonitrile;

2-(1-Hexylmethylamino)acetonitrile;

(S)-2-(2-Heptylmethylamino)acetonitrile;

(R)-3-(2-Heptylmethylamino)propionitrile;

2-(2-Propylamino)ethanephosphonic acid;

(R)-2-(2-Pentylamino)ethanephosphonic acid;

(S)-2-(2-Heptylamino)ethanephosphonic acid;

2-(2-Propylmethylamino)ethanephosphonic acid;

(S)-2-(2-Heptylmethylamino)ethanephosphonic acid; and

(R)-2-(2-Heptylamino)ethane-5-tetrazole.

Compounds of formula I which are optically pure enantiomers are novel. Achiral and racemic compounds are novel with the exception of the following exclusions, although their properties as cellular rescue agents are not known.

a) for X = COOH; n = 1; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = H$ and m = 1 to 4, 6, 7, 9, 11, or 13, and

$R_2 = CH_3$ and m= 0, 1 or 2.

b) for X= COOH; n = 1; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:

$R_2 = H$ and m = 2 or 3, and

$R_2 = CH_3$ and m = 0.

c) for X = $COOR_5$; n = 1; $R_3 = R_4$ = H, exclude compounds for which:

R_2 = H and m = 1 to 4, or 9, and

$R_2 = CH_3$ and m = 0 or 1, and

R_5 = methyl, ethyl, t-butyl.

d) for X = COOH; n = 2; $R_3 = R_4$ = H, exclude compounds for which:

R_2 = H and m = 1 to 4, 6, 9 or 11, and

$R_2 = CH_3$ and m = 0, 1 or 4.

e) for X = COOH; n = 2; R_3 = H; $R_4 = CH_3$, exclude compounds for which:

R_2 = H and m = 1 or 2.

f) for X = $COOR_5$; n = 2; $R_3 = R_4$ = H, exclude compounds for which:

R_2 = H and m = 1 to 5, 9 or 15,

$R_2 = CH_3$ and m = 0 or 1, and

R_5 = methyl, ethyl, t-butyl.

g) for X = $COOR_5$; n = 2; R_3 = H; $R_4 = CH_3$, exclude compounds for which:

R_2 = H and m = 1 or 2,

$R_2 = CH_3$ and m = 0, and

R_5 = methyl, ethyl, t-butyl.

h) for X = COOH; n = 3; $R_3 = R_4$ = H, exclude compounds for which:

R_2 = H and m = 2 or 6.

i) for X = $COOR_5$; n= 3; $R_3 = R_4$ = H, exclude compounds for which:

R_2 = H and m = 2,

$R_2 = CH_3$ and m = 0 or 1, and

R_5 = methyl, ethyl, t-butyl.

j) for X = C≡N (cyano); n = 1; $R_3 = R_4$ = H, exclude compounds for which:

R_2 = H and m = 1, 2, 4, 5 or 6, and

$R_2 = CH_3$ and m = 0, 1 or 2.

k) for X = C≡N; n = 1; R_3 = H; $R_4 = CH_3$, exclude compounds for which:

R_2 = H and m = 1, and

$R_2 = CH_3$ and m = 0.

l) for X = C≡N; n = 2; $R_3 = R_4$ = H, exclude compounds for which:

R_2 = H and m = 1, 2, 3, 4 or 6, and

$R_2 = CH_3$ and m = 0, 1 or 4.

m) for X = C≡N; n = 2; R_3 = H; $R_4 = CH_3$, exclude compounds for which:

R_2 = H and m = 2, and

$R_2 = CH_3$ and m = 0.

n) for X = C≡N; n = 3; $R_3 = R_4$ = H, exclude compounds for which:

R_2 = H and m = 1 to 4, and

$R_2 = CH_3$ and m = 1 or 2.

o) for X = PO_3H_2; n = 2; $R_3 = R_4$ = H, exclude compounds for which:

$R_2 = CH_3$ and m = 0, 1 or 5.

p) for X = $PO_3(R_5)_2$; n = 2; $R_3 = R_4$ = H, exclude compounds for which:

$R_2 = CH_3$ and m = 0 or 1, and

R_5 = ethyl.

q) for X = 5-tetrazole; n = 2; $R_3 = R_4$ = H, exclude compounds for which:

$R_2 = CH_3$ and m = 0.

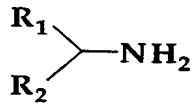
Particularly preferred are those of the R and S configurations, depending on the subclass of compound. Methods of resolving the racemates are known. Suitable methods include fractional crystallization, derivatization of the racemate followed by stereospecific enzymatic removal of the attached group, and chromatography. It is preferred, however, to make chiral compounds of formula I from chiral reactants, using reactions that do not destroy the stereochemistry. When referring to enantiomers, it is preferred that an enantiomer shall not contain more than 3% of the compound of the opposite configuration. It is particularly preferred that an enantiomer contain less than 1% of the corresponding enantiomer of the opposite configuration.

Some of the inactive enantiomers for a given class or subclass of compounds strongly antagonize the antiapoptotic actions of the active enantiomers, and are useful as research tools.

The invention extends to salts of compounds of formula I. For administration the salts should be pharmaceutically acceptable, but other salts may be useful, for example, in synthesis or for purification.

Methods of Preparing Compounds of the Invention

Compounds of the invention can be prepared in a variety of different ways. One process involves the addition of a primary amine of formula (II)



(II)

across the olefinic double bond of α,β-unsaturated carboxylic acid esters (such as methyl acrylate), of vinylphosphonic acids esters or of α,β-unsaturated nitriles (such as acrylonitrile) of formula (III)[21],

(III)

wherein X is a polarized group such as carboxylic ester, phosphonic ester or nitrile to give the corresponding N-alkylamino propionic esters, ethanephosphonic esters and propionitriles.

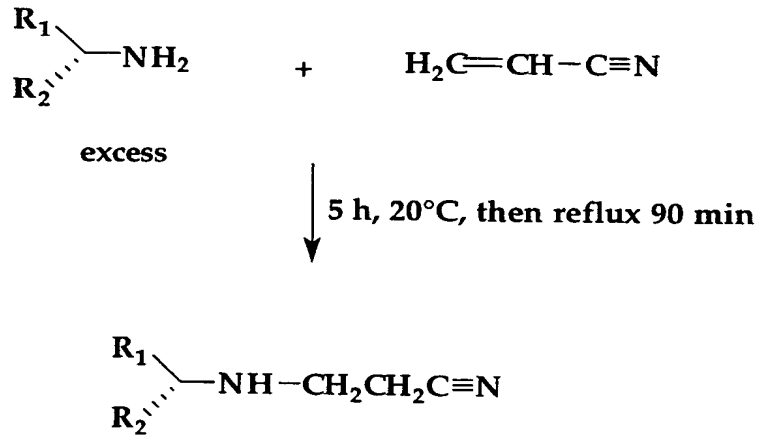
It is possible to use an amine of the formula (II) in which R_1 differs from R_2 in the form of a racemate and to separate the enantiomers subsequently, but it is preferred to use an amine in substantially enantiomerically pure form.

Chiral primary amines (R- or S- forms) were prepared by recrystallization of the tartrates of the racemates from methanol [22], except for (R) and (S)-2-butylamines which were purchased from Aldrich Chemical

Co. Enantiomeric purity was determined using gas chromatography with a chiral capillary column and chiral derivatizing agent [23]. In analogy to the above, chiral primary amines can also be added to the C-C double bond of methyl acrylate, diethyl vinylphosphonate or acrylonitrile to give the corresponding chiral methyl N-alkylaminopropionate, chiral diethyl N-alkylaminoethanephosphonate or chiral N-alkylaminopropionitrile.

In one embodiment, an excess of a chiral amine adds to the olefinic bond of acrylonitrile, as depicted in the following scheme.

Excess Amine and Acrylonitrile:



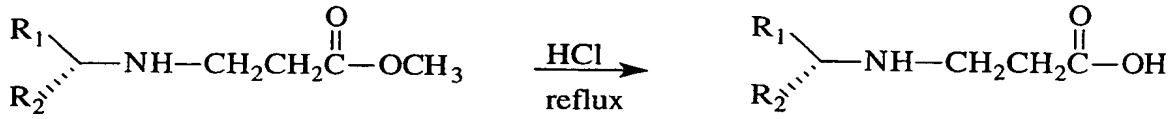
where R_1 = hydrogen, methyl or ethyl and
R_2 = methyl, ethyl, propyl, butyl, pentyl, hexyl.

In another embodiment an excess of the amine can be added to the olefinic double bond of diethyl vinylphosphonate to give the corresponding diethyl N-alkylaminoethanephosphonate. Hydrochloric acid hydrolysis of the aminophosphonic diester yields the corresponding aminophosphonic acid as the hydrochloride salt.

In yet another embodiment an excess of the amine can be added to the olefinic double bond of methyl acrylate to give the corresponding methyl N-alkylaminopropionate [24]. Hydrolysis of the carboxylate ester

with hydrochloric acid produces an amino acid as its hydrochloride salt, in accordance with the following reaction scheme:

Hydrolysis of Esters:

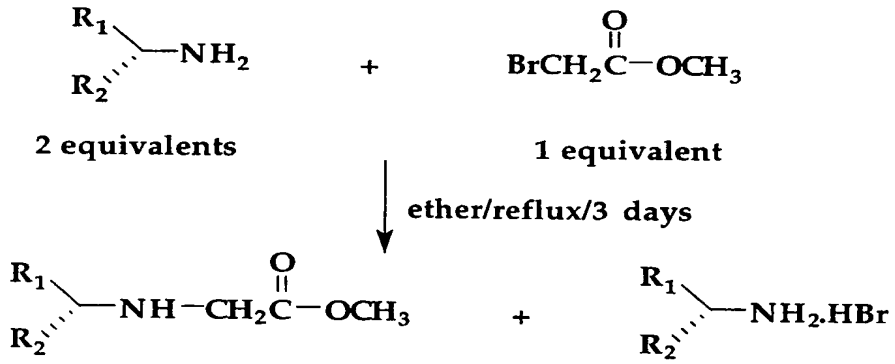


A second process to give compounds of the invention which contain only one carbon atom between the nitrogen atom and the functional group involves condensing a primary aliphatic amine of formula (II) with a bromomethyl reactant of formula (IV)

$$LCH_2X \qquad (IV)$$

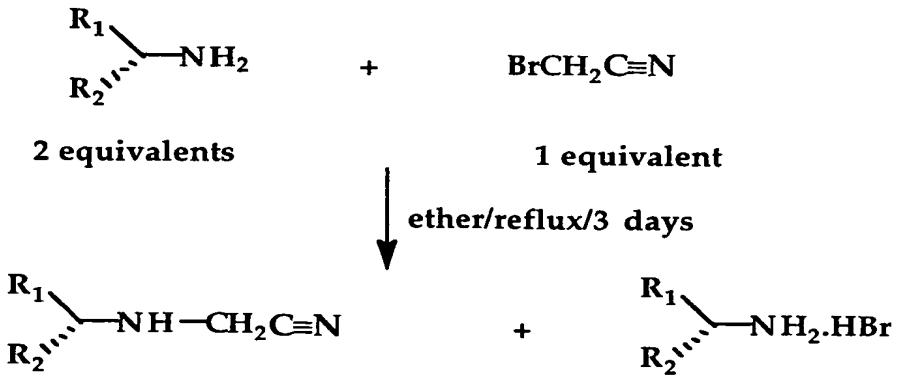
wherein L is a leaving group, for example a halide, tosyl or mesyl group (bromide is preferred), and X is carboalkoxy (carbomethoxy or carbethoxy is preferred), nitrile or phosphodiethoxy. Again, the amine can be used in racemic or enantiomerically pure form. In one preferred embodiment, two equivalents of the amine are reacted with one equivalent of the bromomethyl analogue of formula (IV) to form the required aminomethanecarboxylate (glycine) ester and the hydrobromide salt of the amine, which can be isolated and reused, in accordance with the following reaction scheme.

Two Equivalents of Amine and One Equivalent of Bromomethyl Ester in Ether:



In another preferred embodiment, two equivalents of the amine are reacted with one equivalent of the bromomethyl analogue of formula (IV) to form the required aminomethane nitrile (aminoacetonitrile) and the hydrobromide salt of the amine, which can also be isolated and reused, in accordance with the following reaction scheme.

Two Equivalents of Amine and One Equivalent of Bromoacetonitrile in Ether:



Another route to compounds of the invention involves trifluoroacetylation of the amine, followed by reaction with bromomethyl,

bromoethyl or bromopropyl analogues of esters of carboxylic acids or nitriles of formula (V).

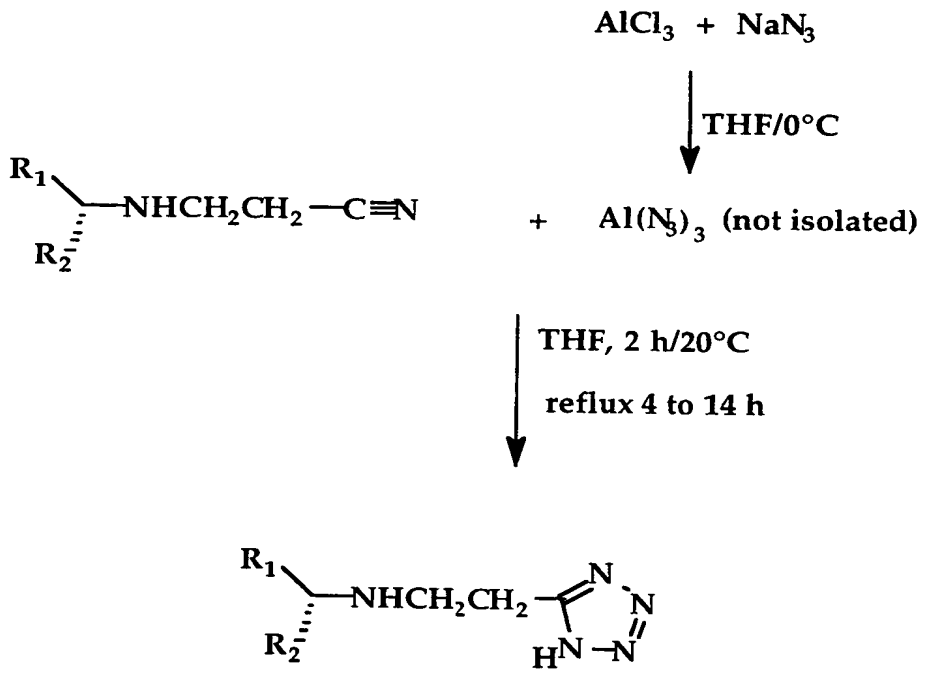
$$L(CH_2)nX \qquad (V)$$

wherein L is a leaving group, for example a halide, tosyl or mesyl group (bromide is preferred), n is 1, 2 or 3 and X is carboalkoxy (methoxy or ethoxy is preferred), nitrile or phosphodiethoxy.

The amine can be used in racemic or enantiomerically pure form. The amine is reacted with trifluoroacetic anhydride or a trifluoroacetyl halide in an inert organic solvent, for instance a chlorinated hydrocarbon such as methylene dichloride, chloroform or carbon tetrachloride, and a base, for example an organic base such as triethylamine. The N-trifluoroacetylamine is then refluxed with a bromo compound of formula (V), suitably in the presence of a base such as potassium t-butoxide in a polar solvent, for example acetonitrile, and in the presence of a crown ether catalyst, for example 18-crown-6. The product of this reaction is then hydrolyzed, suitably by reaction with a base such as an alkali metal hydroxide in an alcoholic solution.

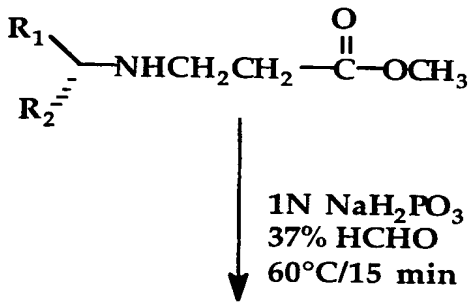
Tetrazole compounds of the invention were prepared by the addition of azide ion to a nitrile triple bond [25]. Again, the amine can be used in racemic or enantiomerically pure form. In one preferred embodiment azide ion is generated by the slow addition of aluminum chloride to a solution/suspension of sodium azide in tetrahydrofuran at 0°C. To the resulting solution of aluminum azide is added the nitrile (prepared as in the pathways described above) in tetrahydrofuran at room temperature, followed by stirring for 2 hours and then gentle refluxing for several hours, according to the following scheme.

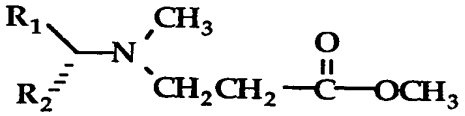
Addition of Azide Ion to Nitrile:



N-Methylation of the various secondary amines described above is achieved by reductive methylation using formaldehyde and sodium phosphite [26]. Again, the amine can be used in racemic or enantiomerically pure form. An amino carboxylate ester or amino nitrile (as the hydrochloride salt or free base) is dissolved in aqueous sodium dihydrogen phosphite and reacted with an excess of 37% aqueous formaldehyde at 60°C for 15 min. The product is isolated by ether extraction after basification of the ice-cold reaction mixture with sodium hydroxide. A preferred embodiment is shown in the following reaction scheme.

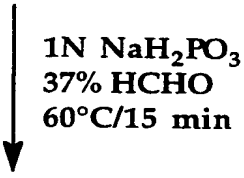
N-Methylation of an Amino Ester:

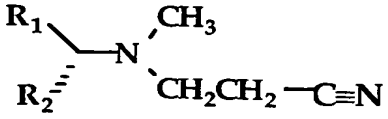




Yet another preferred embodiment is shown in the following reaction scheme.

N-Methylation of an Amino Nitrile:





Therapeutic Methods of the Invention

As hereinbefore mentioned, the compounds of the formula I (as described above) have many therapeutic applications.

In one aspect, the present invention provides a method for treating or preventing a condition wherein cell death occurs by apoptosis comprising administering an effective amount of a compound of the formula I to an animal in need thereof.

The term "effective amount" as used herein means an amount effective, at dosages and for periods of time necessary to achieve the desired result. The term "animal" as used herein includes all members of the animal kingdom including humans.

In another aspect, the present invention provides a use of a compound of the formula I to treat or prevent a condition wherein cell death occurs by apoptosis.

In yet a further aspect, the present invention provides a use of a compound of the formula I to prepare a medicament to treat or prevent a condition wherein cell death occurs by apoptosis.

Conditions wherein cell death occurs by apoptosis includes, but are not limited to, stroke, head trauma, Bell's palsy, spinal cord and other nerve crush injuries, Alzheimer's disease, Parkinson's disease, Pick's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, cardiac myopathies, nephropathy, retinopathy, diabetic complications, glaucoma, as well as idiopathic neuropathies.

Pharmaceutical Compositions

The compounds of the general formula I may be formulated into pharmaceutical compositions for administration to subjects in a biologically compatible form suitable for administration *in vivo*. The compositions containing the compounds of the invention can be prepared by per se known methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for

example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985). On this basis, the compositions include, albeit not exclusively, solutions of the substances in association with one or more pharmaceutically acceptable vehicles or diluents, and contained in buffered solutions with a suitable pH and iso-osmotic with the physiological fluids.

The active substance may be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), oral administration, inhalation, transdermal application, or rectal administration.

In oral administration, the compounds may be administered as tablets, coated tablets, gelatine capsules, capsules, cachets, and solutions or suspensions to be taken orally. The compounds can also be administered parenterally or through any other suitable administrative route such as intravenous, subcutaneous, depot injections, intramuscular, intrathecal, intraventricular, intra-articular, rectal (suppository, enema), sublingual, buccal, intra-ocular, intra-vitreo, transdermal (skin patch), nasal drops (nebulizer, insufflation), liposomal delivery systems. The daily dosage could likely range from 1 to 100 mg.

Accordingly, in another aspect, the present invention provides a pharmaceutical composition comprising a compound of general formula (I) in admixture with a suitable diluent or carrier. The compound may be achiral or a substantially enantiomerically pure R- or S-enantiomer, or a pharmaceutically acceptable salt thereof, in admixture with pharmaceutically acceptable diluents or carriers. The compositions are useful in the treatment or prevention of conditions in which cell death occurs by apoptosis.

In another aspect, the present invention provides a commercial package containing as active ingredient a compound of the formula I, or a pharmaceutically acceptable salt thereof, together with instructions for its use for the treatment or prevention of a condition in which cell death occurs by apoptosis.

EXAMPLES

Example 1:

In Vitro Protocol for Assessing the Antiapoptotic Capacity of Various Compounds in Cerebellar Granule Cells:

The following biological data demonstrate that the compounds of the invention exhibit antiapoptotic properties.

Cultures of cerebellar granule cells (CGC) can be induced into apoptosis by the addition of a high concentration of cytosine arabinoside (AraC) [27]. It has been shown that this is a p53 dependent apoptosis [28]. We have measured the antiapoptotic effect of some amino acids, amino esters, amino phosphonic acids, amino nitriles and amino tetrazoles using this system.

Cultures of CGC were obtained from 6-8 day old Wistar rat pups. Cultures were grown on glass in 35 mm petri dishes for three days and then used for experiments. Aliquots (20 ul) of drug solutions (AraC, anti-apoptotic drugs, drug vehicles) were added to the medium of the culture. 24 Hours later the cultures were fixed with FAM, and stained with bis-benzamide. Normal and apoptotic nuclei were counted to a total of 90-120 cells per culture. The optimum concentration of AraC was found to be 300 uM.

The results are summarized in Tables 1 - 4.

Table 1 - Rescue by Amino Acids and Esters in the CGC Assay

Compound	10^{-6} M	10^{-9} M	10^{-12} M	Rescue
Glycines (aminoacetic acids)				
2-Propyl	R	X	X	yes
1-Hexyl	X	R	X	yes
R-2-Heptyl	X	X	X	no
S-2-Heptyl	R	R	R	yes
B-Alanines (aminopropionic acids)				
2-Propyl	X	R	R	yes
2-Propyl-N-methyl	R	R	X	yes
R-2-Pentyl	X	X	X	no
1-Hexyl	R	R	R	yes
1-Hexyl-N-methyl	R	R	X	yes
R-2-Heptyl		R	R	yes
R-2-Heptyl-N-methyl	R	R	R	yes
S-2-Heptyl			X	no
B-Alaninates (esters)				
2-Propyl	X	X	X	no
1-Hexyl	X	R	R	yes
R-2-Heptyl-N-methyl	R	R	R	yes

R = rescue; X = no rescue

Table 2 - Rescue by Amino Phosphonic Acids in the CGC Assay

Compound	10^{-6} M	10^{-9} M	10^{-12} M	Rescue
2-Propyl	R	R	R	yes
R-2-Pentyl	R	X	X	yes
1-Hexyl	X	X	X	no
R-2-Heptyl	R*	X	X	yes*
S-2-Heptyl	X	R	R	yes

* The presence of 0.5% S-enantiomer (which is potent at 10^{-12} M) in the R-enantiomer is probably responsible for the apparent rescue by the R-enantiomer at 10^{-6} M.

Table 3 - Rescue by Amino Tetrazoles in the CGC Assay

Compound	10^{-6} M	10^{-9} M	10^{-12} M	Rescue
R-2-Heptyl	R	R	R	yes
S-2-Heptyl	X	X	X	no

Table 4 - Rescue by Amino Nitriles in the CGC Assay

Compound	10^{-6} M	10^{-9} M	10^{-12} M	Rescue
Acetonitriles				
2-Propyl	R	R	R	yes
R-2-Pentyl	X	R	X	yes
S-2-Pentyl	X	X	X	no
1-Hexyl	X	R	R	yes
R-2-heptyl	X	X	X	no
S-2-Heptyl	X	R	R	yes
Propionitriles				
2-Propyl	X	X	X	no
2-Propyl-N-methyl	T	T	X	no
R-2-Pentyl	X	X	X	no
tert-Amyl	X	X	X	no
tert-Amyl-N-methyl	X	X	X	no
3-Pentyl	R	R	X	yes
1-Hexyl	X	X	X	no
1-Hexyl-N-methyl	X	X	X	no
R-2-Heptyl	X	R	R	yes
R-2-Heptyl-N-methyl	X	R	X	yes
S-2-heptyl	X	X	X	no

R = rescue; X = no rescue; T = toxic

Detailed Synthetic Procedures

The following non-limiting examples of synthetic procedures are provided.

Example 2:

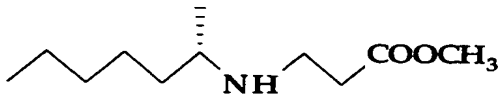
Methyl 3-(1-hexylamino)propionate hydrochloride [Methyl N-(1-hexyl)-β-alaninate]

To ice-water-cooled 1-hexylamine (7.58 g, 75 mmol) was added dropwise methyl acrylate (4.3 g, 50 mmol). After completion of the addition the temperature was allowed to rise to room temperature and the reaction solution was stirred for 5 hours, then refluxed for 90 minutes. After stirring overnight at 20°C the product, methyl 3-(1-hexylamino)propionate, was distilled (b.p. = 85-88°C/2 mm; lit. b.p. 80-84°C/0.5 mm) as a clear, colorless liquid in a yield of 55%. The hydrochloride salt was prepared by the addition of methanolic HCl (15%) to an ethereal solution of the free base; m.p. = 204-205°C (lit. m.p. 190-192°C).

Mass spectrum: m/e: 187 (M+); 116 (M-C_5H_{11}); 84.

Example 3:

(R)-Methyl 3-(2-heptylamino)propionate hydrochloride [(R)-Methyl N-(2-heptyl)-β-alaninate]



Prepared according to Example 2. The hydrochloride salt was recrystallized from methanol/ether; m.p. = 89.5-90.5°C.

Mass spectrum: m/e: 201 (M+); 186 (M-CH_3); 130 (M-C_5H_{11})

Example 4:

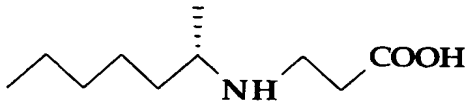
Methyl 3-(2-propylamino)propionate hydrochloride [Methyl N-(2-propyl)-β-alaninate]

Prepared according to Example 2. The hydrochloride salt was crystallized from methanol/ether; m.p. = 108-110°C (lit. m.p. 107°C).

Mass spectrum: m/e: 145 (M+); 130 (M-CH_3); 98; 72; 56.

Example 5:

(R)-3-(2-Heptylamino)propionic acid hydrochloride [(R)-N-(2-heptyl)-β-alanine]



(R)-3-(2-Heptylamino)propionitrile (7.5 g, 44.6 mmol) (prepared according to Example 18) was refluxed with concentrated hydrochloric acid (50 mL) for 4 h. After filtration of insoluble ammonium chloride, the aqueous solution was rotary evaporated to dryness. The residue was stirred with dichloromethane (120 mL) for 2 hours and the insoluble ammonium chloride was filtered. The filtrate was concentrated, filtered again and then evaporated to give a colorless oil which crystallized on cooling. The yield of white hygroscopic product was quantitative; m.p. = 57-58°C.

Mass spectrum: m/e: 187 (M+); 172 (M-CH_3); 116 (M-C_5H_{11}); 72.

1H-NMR (D_2O, 300 MHz): 0.72 (t, 3H); 1.18 (d, 3H); 1.1-1.3 (m, 6H); 1.42/1.60 (2m, 1H each); 2.67 (t, 2H); 3.17 (m, 3H; αCH & CH_2COOH).

The title compound can also be prepared by hydrochloric acid hydrolysis of the methyl ester (prepared according to Example 3).

Example 6:

(S)-3-(2-Heptylamino)propionic acid hydrochloride [(S)-N-(2-heptyl)-β-alanine]

Prepared according to Example 5. The hydrochloride salt, m.p. = 56-58°C, is hygroscopic.

Mass spectrum: m/e: 187 (M+); 172 (M-CH_3); 128 (M-CH_2COOH); 116 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.75 (t, 3H); 1.18 (d, 3H); 1.1-1.3 (m, 6H); 1.45/1.60 (2m, 1H each); 2.68 (t, 2H); 3.20 (m, 3H; αCH & CH_2COOH).

Example 7:

3-(1-Hexylamino)propionic acid [N-(1-hexyl)-β-alanine]

Methyl 3-(1-hexylamino)propionate hydrochloride (see Example 2 for preparation) was hydrolyzed by refluxing in 2N HCl for 24 hours followed by evaporation to dryness; m.p. = 95-97°C (no lit. value).

Mass spectrum: m/e: 173 (M+); 102 (M-C_5H_{11}); 84; 72.

1H-NMR (D_2O, 300 MHz): 0.73 (t, 3H); 1.17 (m, 6H); 1.52 (m, 2H); 2.68 (t, 2H); 2.93 (t, 2H); 3.18 (t, 2H).

Example 8:

3-(2-Propylamino)propionic acid hydrochloride [N-(2-propyl)-β-alanine]

Prepared by hydrolysis of the ester (Example 7). The product is a white powder, m.p. = 154-155°C (no lit. value).

Mass spectrum: m/e: 131 (M+); 116 (M-CH_3); 98; 56.

1H-NMR (D_2O, 300 MHz): 1.20 (d, 6H); 2.70 (t, 2H); 3.19 (t, 2H); 3.32 (m, 1H).

Example 9:

Ethyl 2-(2-propylamino)acetate hydrochloride [Ethyl N-(2-propyl)glycinate]

To a solution of 2-propylamine (4.4 g, 75 mmol) in ether (100 mL) was added ethyl bromoacetate (6.26g, 37.5 mmol). The solution was stirred at 20°C for 3 days. The precipitated 2-propylamine hydrobromide was filtered and the filtrate rotary evaporated to give 5.4 g a clear pale yellow liquid (crude yield = 99%). The hydrochloride salt was prepared and recrystallized from ethanol/ether; m.p. = 120-121°C (no lit. value).

Mass spectrum: m/e: 145 (M+); 130 (M-CH_3); 72 (M-$COOC_2H_5$).

Example 10:

2-(2-Propylamino)acetic acid hydrochloride [N-(2-Propyl)glycine]

The sample was prepared from the nitrile (prepared according to Example 25) in 72% yield using a hydrolysis procedure similar to that

described in Example 12. The hydrochloride salt was recrystallized from acetone; m.p. = 180-184°C (lit. m.p. 203-204.5°C; 182-183°C).

Mass spectrum: (CI). 118 (M+1); 102 (M-CH_3); 72 (M-CO_2H); (EI). 117 (M+); 102 (M-CH_3); 72 (M-COOH).

1H-NMR (D_2O, 300 MHz): 1.19 (d, 6H); 3.33 (m, 1H); 3.79 (s, 2H).

Example 11:

2-(1-Hexylamino)acetic acid hydrochloride [N-(1-Hexyl)glycine] 1HxActAc

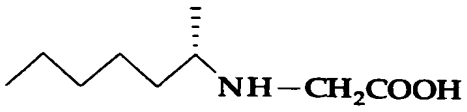
The sample was prepared from the nitrile (procedure analogous to that described in Example 10) in 72% yield using a hydrolysis procedure similar to that described in Example 12. The hydrochloride salt was recrystallized from acetone; m.p.= 162-164°C (lit. m.p. 215-218°C).

Mass spectrum: m/e: 159 (M+); 114 (M-CO_2H); 88 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.72 (t, 3H); 1.20 (m, 6H); 1.55 (m, 2H); 2.96 (t, 2H); 3.77 (s, 2H).

Example 12:

(R)-2-(2-Heptylamino)acetic acid hydrochloride [(R)-N-(2-Heptyl)glycine]



A solution of (R)-2-(2-heptylamino)acetonitrile (1.20 g, 7.79 mmol) (prepared according to Example 23) in concentrated HCl (12 mL) and water (5 mL) was heated for 48 hours at 90°C. After cooling to room temperature, the reaction mixture was concentrated to dryness, filtered, and washed with ethanol to remove NH_4Cl. The resulting filtrate was concentrated to give a crude product (1.40 g). A solution of the crude product (0.60 g) in concentrated HCl (20 mL) and water (10 mL) was heated for 24 hours at 90°C. After cooling to room temperature, the reaction mixture was taken to dryness and triturated in ether to give the hydrochloride salt as a crystalline solid (0.60 g, overall 37% yield); m.p.= 162-164°C.

Mass spectrum: m/e: (CI). 174 (M+1); 158 (M-CH_3); 102 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.74 (t, 3H); 1.18 (d, 3H); 1.1-1.3 (m, 6H); 1.45/1.60 (2m, 1H each); 3.21 (m, 1H); 3.79 (s, 2H).

Example 13:

(S)-2-(2-Heptylamino)acetic acid hydrochloride [(S)-N-(2-Heptyl)glycine]

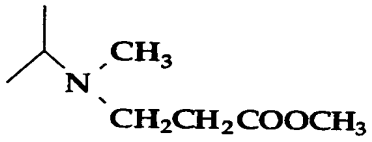
The product was prepared as described in Example 12 in 72% overall yield by hydrolysis of the nitrile hydrochloride salt; m.p.= 161-163°C.

Mass spectrum: m/e: (CI). 174 (M+1); 156 (M-OH); 128 (M-CO_2H).

1H-NMR (D_2O, 300 MHz): 0.73 (t, 3H); 1.18)d, m; 9H); 1.47, 1.60 (2m, 1H each); 3.21 (m, 1H); 3.78 (s, 2H).

Example 14:

Methyl 3-(2-propylmethylamino)propionate hydrochloride [Methyl N-(2-propyl)-N-methyl-β-alaninate]



To a solution of methyl 3-(2-propylamino)propionate hydrochloride (Example 10)(0.907 g; 5 mmol) in 1N sodium dihydrogen phosphite (25 mL) was added 37% formaldehyde (2.1 mL, 23 mmol). The solution was stirred at 60°C for 10 min, then cooled in an ice-water bath and basified with 10% sodium hydroxide (10 mL). The resulting solution was saturated with sodium chloride (9 g) and immediately extracted with ether (3 x 15 mL). The combined filtrates were dried over anhydrous magnesium sulfate and evaporated to dryness to give a clear colorless liquid. The hydrochloride salt, prepared by the addition of methanolic HCl to an ether solution of the free base, precipitated as a viscous oil in 83 % yield.

Mass spectrum: m/e: 159 (M+); 144 (M-CH_3); 86 (M-CH_2COOCH_3).

Example 15:

(R)-Methyl 3-(2-heptylmethylamino)propionate hydrochloride [(R)-Methyl N-(2-heptyl)-N-methyl-β-alaninate]

The hydrochloride salt was obtained in 93% yield as a colorless viscous liquid.

Mass spectrum: m/e: 215 ((M+); 200 (M-CH_3); 144 (M-C_5H_{11}).

Example 16:

(R)-3-(2-Heptylmethylamino)propionic acid hydrochloride [N-(2-Heptyl)-N-methyl-β-alanine]

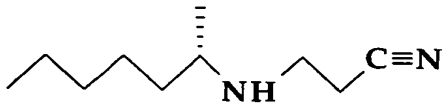
The hydrochloride salt precipitated as a colorless, viscous oil.

Mass spectrum: m/e: 201 (M+); 186 (M-CH_3); 130 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.72 (t, 3H); 1.18 (m, 9H); 1.47, 1.59 (2m, 1H each); 2.65 (d, 3H); 2.74 (t, 2H); 3.11 (m, 1H); 3.34 (m, 2H).

Example 17:

(R)-3-(2-Heptylamino)propionitrile hydrochloride



To ice-water-cooled (R)-2-heptylamine (99.4% R)(9.28 g, 80.7 mmol) was added dropwise acrylonitrile (2.85 g, 3.543 mL, 54 mmol). After completion of the addition the temperature was allowed to rise to room temperature and the reaction solution was stirred for 5 hours, then refluxed for 90 minutes. After stirring overnight at 20°C the product, (R)-3-(2-heptylamino)propionitrile, was distilled as a clear, colorless liquid, b.p. = 101-102°C/2 mm, with a yield of 85%. The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the free base; m.p. = 134-135°C.

Mass spectrum: m/e: (CI) 169 (M+H)+; 153 (M-CH_3); 97 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.73 (t, 3H); 1.20 (d, m; 9 H); 1.45, 1.61 (2m, 1H each); 2.85 (t, 2H); 3.3 (m, 3H).

Elemental Analysis: Calculated: %C = 58.66; %H = 10.34; %N = 13.68.

Found: %C = 58.73; %H = 10.53; %N = 13.47.

The starting material, (R)-2-heptylamine, was resolved from the racemate by repeated recrystallizations of its L-tartrate salt from methanol. Eight recrystallizations using a ratio of volume (of methanol) to weight (of tartrate salt) of 2.4 to 2.6 (increasing as optical purity increased) gave the R-enantiomer with an optical purity of 99.4% R. The optical purity was assessed by derivatization with freshly prepared chiral reagent (S)-N-trifluoroacetylprolyl chloride and then gas chromatography on a chiral column [23].

Example 18:

(S)-3-(2-Heptylamino)propionitrile hydrochloride

(S)-2-Heptylamine as its D-tartrate salt was prepared by recrystallization of the racemate (S-enriched, isolated and prepared from the combined filtrates of the R-enantiomer L-tartrate recrystallizations described in Example 17) . The optical purity was 99.4% S. S-2HECN was prepared in 85% yield (b.p. 99-100°C/2 mm) as described for the R-enantiomer in Example 17. The hydrochloride salt was recrystallized from methanol/ether; m.p. = 133-134°C.

Mass spectrum: m/e: (CI) 169 (M+H)+; 153 (M-CH3); 128 (M-CH_2CN); 97 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.72 (t, 3H); 1.20 (d, m; 9H); 1.45, 1.62 (2m, 1H each); 2.85 (t, 2H); 3.29 (m, 3H).

Elemental Analysis: Calculated: %C = 58.66; %H = 10.34; %N = 13.68.

Found: %C = 58.61; %H = 10.10; %N = 13.42.

Example 19:

3-(2-Propylamino)propionitrile hydrochloride

The free base, b.p. = 94°C/30 mm (lit. b.p. 86-87°C/17 mm), was prepared according to the procedure in Example 17 and then converted to the hydrochloride salt which was recrystallized from methanol/ether; m.p. = 145.5-146°C (no lit. value).

Mass spectrum: m/e: 140 (M+); 97 (M-CH_3); 72 (M-CH_2CN).

1H-NMR (D_2O, 300 MHz): 1.20 (d, 6H); 2.85 (t, 2H); 3.29 (t, 2H); 3.36 (m, 1H).

Example 20:

3-(1-Hexylamino)propionitrile hydrochloride

The hydrochloride salt was recrystallized from ethanol/ether; m.p. = 188-189°C (no lit. value).

Mass spectrum: m/e: 154 (M+); 114 (M-CH_2CN); 83 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.72 (t, 3H); 1.18 (m, 6H); 1.53 (m, 2H); 2.87 (t, 2H); 2.96 (t, 2H); 3.29 (t, 2H).

Example 21:

3-(3-Pentylamino)propionitrile hydrochloride

The free base, b.p. = 84-85°C/2 mm (no lit. value), was converted to the hydrochloride salt, m.p. = 118.5-119.5°C (no lit. value).

Mass spectrum: m/e: 140 (M+); 111 (M-C_2H_5); 100 (M-CH_2CN); 82; 70.

1H-NMR (D_2O, 300 MHz): 0.83 (t, 6H); 1.64 (m, 4H); 2.89 (t, 2H); 3.10 (m, 1H); 3.33 (t, 2H).

Example 22:

3-(t-Amylamino)propionitrile hydrochloride

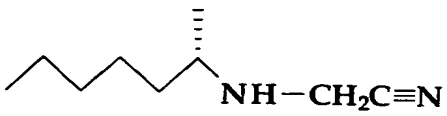
The free base, b.p. = 62-63°C/2 mm (no lit. value), was converted to the hydrochloride salt, m.p. = 199-200°C (no lit. value).

Mass spectrum: m/e: 140 (M+, absent); 125 (M-CH_3); 111 (M-CH_2CH_3)

1H-NMR (D_2O, 300 MHz): 0.82 (t, 3H); 1.20 (s, 6H); 1.58 (q, 2H); 2.83 (t, 2H); 3.29 (t, 2H).

Example 23:

(R)-2-(2-Heptylamino)acetonitrile hydrochloride



To a solution of (R)-2-heptylamine (1.90 g, 16.5 mmol) in ether (25 mL) were added anhydrous Na_2CO_3 (1.60 g, 14.9 mmol), and bromoacetonitrile (0.92 mL, 13.2 mmol). The reaction mixture was stirred at

room temperature for 24 hours, and for another 14 hours at 80°C. After cooling to room temperature, the reaction mixture was filtered and the filtrate washed with HCl (3 N, 3x10 mL). The aqueous layer was basified with NaOH (6 N) and extracted with ether (3x25 mL). The resulting ethereal solution was dried over Na_2SO_4, and evaporated to dryness. The residue was fractionated by flash column chromatography (25% EtOAc/hexane, ether) to give a colorless oil (2.10 g, 82%). The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the free base; m.p = 152-3°C.

Mass spectrum: m/e: (CI).155 (M+1); 128 (M-CN); (EI) 139 (M-CH_3); 83 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.75 (t, 3H); 1.20 (d, 3H); 1.15-1.35 (m, 6H); 1.47/1.62 (2m, 1H each); 3.35 (m, 1H); 4.18 (s, 2H).

Elemental Analysis: Calculated: %C = 56.68; %H = 10.04; %N = 14.69.

Found: %C = 56.81; %H = 10.20; %N = 14.46.

Example 24:

(S)-2-(2-Heptylamino)acetonitrile hydrochloride

The sample was prepared in 96% yield using the above-described procedure (Example 23). The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the free base and was recrystallized from ethanol/ether. The salt sublimes during melting; m.p. = 140°C.

Mass spectrum: m/e: 154 (M+);139 (M-CH_3).

1H-NMR (D_2O, 300 MHz): 0.73 (t, 3H); 1.18 (d, m; 9 H); 1.43, 1.59 (2m, 1H each); 3.31 (m, 1H); 4.15 (s, 2H).

Elemental Analysis: Calculated: %C = 56.68; %H = 10.04; %N = 14.69.

Found: %C = 56.51; %H = 9.71; %N = 14.79.

Example 25:

2-(2-Propylamino)acetonitrile hydrochloride

The hydrochloride salt was recrystallized from methanol/ether; m.p. = 166-167°C (lit. m.p. 154-156°).

Mass spectrum: m/e: 98 (M+); 83 (M-CH_3); 56.

1H-NMR (D_2O, 300 MHz): 1.19 (d, 6H); 3.45 (m, 1H); 4.17 (s, 2H).

Example 26:

2-(1-Hexylamino)acetonitrile hydrochloride

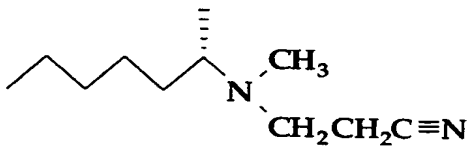
The free base of the sample was prepared in 62% yield using the above-described procedure (Example 23). The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the free base, and was recrystallized from ethanol/ether; m.p.= 114-115°C (lit. m.p. 84-86°C).

Mass spectrum: m/e: (CI).141 (M+1)+; 126 (M-CN).

1H-NMR (D_2O, 300 MHz): 0.74 (t, 3H); 1.21 (m, 6H); 1.58 (m, 2H); 3.08 (t, 2H); 4.17 (s, 2H).

Example 27:

(R)-3-(2-Heptylmethylamino)propionitrile hydrochloride



(R)-3-(2-Heptylamino)propionitrile (Example 17) (0.85 g, 5.0 mmol) was dissolved in 1N sodium dihydrogen phosphite (NaH_2PO_3)(25 mL) and 37% formaldehyde (2.1 mL, 23 mmol) was added. Sufficient dioxan was added to give a clear solution (10 mL). The solution was stirred at 60°C for 15 min during which time it became cloudy. To the cooled solution was then added 20% sodium hydroxide (20 mL) and sodium chloride (9 g). The basic solution was extracted with ether (3 x 15 mL). The combined extracts were dried over anhydrous magnesium sulfate and then evaporated to give a clear, colorless liquid in quantitative yield. The hydrochloride salt was prepared by adding methanolic HCl to an ether solution of the free base; m.p. = 98-98.5°CC. Overall yield was 85%.

Mass spectrum: m/e: 182 (M+); 167 ($M-CH_3$); 142 ($M-CH_2CN$); 111 ($M-C_5H_{11}$).

1H-NMR (D_2O, 300 MHz): 0.77 (t, 3H); 1.20 (d, 3H); 1.15-1.35 (m, 6H); 1.50/1.62 (2m, 1H each); 2.73 (s, 3H); 2.95 (t, 2H); 3.40 (m, 3H; aCH & CH_2CN).

Elemental Analysis: Calculated: %C = 60.39; %H = 10.60; %N = 12.80.

Found: %C = 59.55; %H = 10.29; %N = 13.67.

Example 28:

3-(2-Propylmethylamino)propionitrile hydrochloride

The hydrochloride salt was obtained in 90% yield; m.p. = 121-121.5°C (no lit. value)(see Example 27).

Mass spectrum: m/e: 126 (M+); 111 (M-CH_3); 86 (M-CH_2CN).

1H-NMR (D_2O, 300 MHz): 1.23 (d, 6H); 2.73 (s, 3H); 2.97 (t, 2H); 3.52 (br s, 2H); 3.60 (m, 1H).

Example 29:

3-(t-Amylmethylamino)propionitrile hydrochloride

The hydrochloride salt was obtained in 87% yield; m.p. = 137-138°C (no lit. value)(see Example 27).

Mass spectrum: m/e: 154 (M+); 139 (M-CH_3); 125 (M-C_2H_5); 72.

1H-NMR (D_2O, 300 MHz): 0.87 (t, 3H); 1.25 (6H); 1.67 (q, 2H); 2.10 (s, 2H); 2.73 (s, 3H); 2.94 (broad t, 2H).

Elemental Analysis: Calculated: %C = 56.68; %H = 10.04; %N = 14.69.

Found: %C = 56.62; %H = 10.12; %N = 14.62.

Example 30:

3-(1-Hexylmethylamino)propionitrile hydrochloride

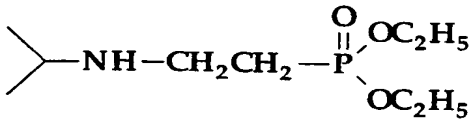
The hygroscopic hydrochloride salt was obtained in 75% yield; m.p. = 77-78.5°C (no lit. value)(see Example 27).

Mass spectrum: m/e: 168 (M+); 128 (M-CH_2CN); 97 (M-C_5H_{11}).

1H-NMR (D_2O, 300 MHz): 0.72 (t, 3H); 1.20 (m, 6H); 1.60 (m, 2H); 2.79 (s, 3H); 2.95 (t, 2H); 3.09 (t, 2H); 3.42 (t, 2H).

Example 31:

Diethyl 2-(2-propylamino)ethanephosphonate hydrochloride



To ice-cooled 2-propylamine (0.53 mL, 6.2 mmol) was added dropwise diethyl vinylphosphonate (0.4 mL, 3.1 mmol) under N_2. The reaction mixture was stirred for 2 hours at 0°C, for 14 hours at room temperature, and for 10 hours at 100°C. After cooling to room temperature, the reaction mixture was concentrated to give a colorless oil (0.89 g). To a solution of the crude product (0.89 g) in ether (40 mL) was added ethanolic HCl (15%), and then stirred for 2 hours at room temperature. The resulting crystallized hydrochloride salt was filtered, washed with ether to give a white solid (0.76 g, overall 95%); m.p. = 96-97°C (no lit. value).

Mass spectrum: m/e: 208 (M-CH_3)+; 180 (M-C_3H_7)+.

Example 32:

2-(2-Propylamino)ethanephosphonic acid hydrochloride

The hydrochloride salt of the product (starting from the diester, Example 31) was prepared in 32% overall yield using the procedure described in Example 37; m.p.= 164-166°C (no lit. value).

Mass spectrum: m/e: (CI). 168 (M+1)+.

1H-NMR (D_2O, 300 MHz): 1.16 (d, 6H); 1.84 (m, 2H); 3.08 (q, 2H); 3.27 (m, 1H).

Example 33:

Diethyl 2-(1-hexylamino)ethanephosphonate hydrochloride

The crude product was prepared in 100% yield using the above-described procedure. The hydrochloride salt of the product was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the product; the salt is a viscous oil.

Mass spectrum: m/e: 265 (M)+, 194 (M-C_5H_{11})+.

Example 34:

2-(1-Hexylamino)ethanephosphonic acid hydrochloride

The hydrochloride salt was prepared by hydrolysis of the diethyl ester using the method described in Example 37; m.p. = 145-150°C (no lit. value).

Mass spectrum: m/e: too involatile

1H-NMR (D_2O, 300 MHz): 0.70 (t, 3H); 1.15 (m, 6H); 1.50 (m, 2H); 1.90 (m, 2H); 2.88 (t, 2H); 3.08 (q, 2H).

Elemental Analysis: Calculated: %C = 39.11; %H = 8.62; %N = 5.70.

Found: %C = 39.34; %H = 8.53; %N = 5.89.

Example 35:

(R)-Diethyl 2-(2-heptylamino)ethanephosphonate hydrochloride

The free base was prepared in 93% yield using the above-described procedure. The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the product; the salt is a viscous oil.

Mass spectrum: m/e: (CI). 280 (M+1)+; 264.(M-CH_3)+; 208 (M-C_5H_{11})+.

Example 36:

(S)-Diethyl 2-(2-heptylamino)ethanephosphonate hydrochloride

The free base was prepared in 91% yield using the above-described procedure. The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the product; the salt is a viscous oil.

Mass spectrum: m/e: (CI). 280 (M+1)+; 208 (M-C_5H_{11})+.

Example 37:

(R)-2-(2-Heptylamino)ethanephosphonic acid hydrochloride

A solution of (R)-diethyl 2-(2-heptylamino)ethanephosphonate hydrochloride (0.19 g, 0.68 mmol) in concentrated HCl (7 mL) was heated at 90°C for 48 hours. The reaction mixture was then evaporated to dryness and the residue triturated with acetone. The white solid was filtered and air-dried giving an 86% overall yield; m.p. = 106-112°C (no lit. value).

Mass spectrum: m/e: too involatile

1H-NMR (D_2O, 300 MHz): 0.73 (t, 3H); 1.25-1.10 (m, 12H); 1.43 (m, 1H); 1.58 (m, 1H);

1.89-1.78 (m, 2H); 3.22-3.05 (m, 3H).

Elemental Analysis: Calculated: %C = 41.62; %H = 8.93; %N = 5.39.

Found: %C = 41.68; %H = 9.10; %N = 5.23.

Example 38:

(S)-2-(2-Heptylamino)ethanephosphonic acid hydrochloride

The hydrochloride salt was prepared in 71% overall yield using the above described procedure; m.p. = 106-113°C (no lit. value).

Mass spectrum: m/e: too involatile

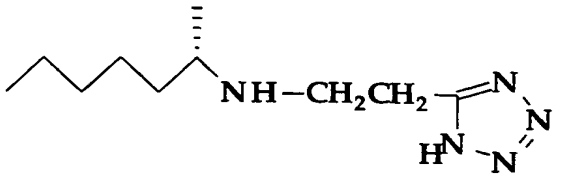
1H-NMR (D_2O, 300 MHz): 0.73 (t, 3H); 1.25-1.10 (m, 12H); 1.44 (m, 1H); 1.59 (m, 1H); 1.89-1.78 (m, 2H); 3.22-3.05 (m, 3H).

Elemental Analysis: Calculated: %C = 41.62; %H = 8.93; %N = 5.39.

Found: %C = 41.43; %H = 9.09; %N = 5.33.

Example 39:

(R)-2-(2-Heptylamino)ethane-5-tetrazole hydrochloride



The compound as its hydrochloride salt was prepared in 28% overall yield using the procedure described below in Example 40; the salt is a viscous oil.

Mass spectrum: m/e: (CI). 140 (M-C_5H_{11})+; 128 (M-$C_2H_3N_4$)+.

1H-NMR (D_2O, 300 MHz): 0.71 (t, 3H); 1.18 (m, 9H); 1.44, 1.60 (2m, 1H each); 3.30 (t+m; 3H); 3.45 (m, 2H).

Example 40:

(S)-2-(2-Heptylamino)ethane-5-tetrazole hydrochloride

To an ice-cooled suspension of NaN_3 (2.60 g, 40 mmol) in dry THF (20 mL) was added $AlCl_3$ (1.36 g, 10 mmol) in portions under N_2, and stirred for 30 minutes. To the resulting suspension was added a solution of (S)-3-(2-heptylamino)propionitrile (1.68 g, 10 mmol) in THF (10 mL), and stirred for 2 hours at 0°C, then gently refluxed for 24 hours. After cooling to room temperature, the reaction mixture was quenched by the careful addition of HCl (3 N, 15 mL), water (5 mL), and the two layers were separated. The lower aqueous layer was extracted with ethyl acetate (3x15 mL). The upper (organic) layer and the organic extracts were combined and dried over Na_2SO_4, then taken to dryness to give crude product (oil, 1.36 g). The oil was diluted with ether (30 mL) and ethanol (5 mL), stirred for two hours, and filtered to give the hydrochloride salt (0.21 g, 9% overall yield); m.p. = 112-113°C (no lit. value).

Mass spectrum: m/e: (CI). 140 $(M-C_5H_{11})+$; 128 $(M-C_2H_3N_4)+$.

1H-NMR (D2O, 300 MHz): 0.72 (t, 3H); 1.20 (d, 3H); 1.15-1.35 (m, 6H); 1.45/1.62 (2m, 1H each); 3.30 (t+m; 3H); 3.43 (m, 2H).

Elemental analysis: Calculated: %C = 48.47; %H = 8.95; %N = 28.27.

Found: %C = 48.24; %H = 8.85; %N = 28.40.

FULL CITATIONS FOR REFERENCES REFERRED TO IN THE SPECIFICATION

1. Ansari, K.S., et al., Rescue of axotomized immature rat facial motoneurons by R(-)-deprenyl: stereospecificity and independence from monoamine oxidase inhibition. Journal of Neuroscience, 1993. **13**: p. 4042-4053.

2. Davis, B.A., et al. Neurorescue by the optically acive enantiomers of some aliphatic N-methylpropargylamines. Abstract, American Society for Neurochemistry. 1995. Santa Monica, CA.

3. Oh, C., et al., (-)-Deprenyl alters the survival of adult murine facial motoneurons after axotomy: Increases in vulnerable C57BL strain but decreases in motor neuron degeneration mutants. J. Neurosci. Res., 1994. **38**: p. 64-74.

4. Paterson, I.A., B.A. Davis, and A.A. Boulton, Aliphatic propargylamines prevent hippocampal neuronal death induced by hypoxia-ischemia. J. Neurochem., 1997. **69 (Supp)**: p. S137.

5. Paterson, I.A., et al., (-)-Deprenyl reduces delayed neuronal death of hippocampal pyramidal cells. Neurosci. Biobehav. Rev., 1997. **21**: p. 181-186.

6. Paterson, I.A., et al., R-Deprenyl and R-2-heptyl-N-methylpropargylamine prevent apoptosis in cerebellar granule neurons induced by cytosine arabinoside but not low extracellular potassium. J. Neurochem., 1998. **98**: p. 515-523.

7. Paterson, I.A., et al., The anti-apoptotic effects of 2HMP is due to a desmethyl metabolite. Society for Neuroscience Abstracts, 1997. **23 (part 2)**: p. 2254 (#880.6).

8. Paterson, I.A., et al., Aliphatic propargylamines as cellular rescue agents. United States Patent, Filed July 14,1997.

9. Tatton, W.G. and C.E. Greenwood, Rescue of dying neurons: a new action for deprenyl in MPTP Parkinsonism. J. Neurosci. Res., 1991. **30**: p. 666-672.

10. Tatton, W.G., et al., (-)-Deprenyl reduces PC12 cell apoptosis by inducing new protein synthesis. J. Neurochem., 1994. **63**: p. 1572-1575.

11. Salo, P.T. and W.G. Tatton, Deprenyl reduces the death of motoneurons caused by axotomy. J. Neurosci. Res., 1992. **31**: p. 394-400.

12. Wu, R.-M., D.L. Murphy, and C.C. Chiueh, Neuronal protective and rescue effects of deprenyl against MPP+ dopaminergic toxicity. J. Neural Transm. [Gen Sect], 1995. **100**: p. 53-61.

13. Yoles, E. and M. Schwartz, N-Propargyl-1 (R)-aminoindan (TVP-1012), a putative neuroprotective agent, enhance in vitro neuronal survival after glutamate toxicity. Abstract, American Society for Neuroscience. 1995. San Diego, CA.

14. Zhang, X., et al., Immunohistochemical evidence of neuroprotection by R-(-)-deprenyl and N-(2-hexyl)-N-methylpropargylamine on DSP-4-induced degeneration of rat brain noradrenergic axons and terminals. Journal of Neuroscience Research, 1996. **43**: p. 482-489.

15. Yu, P.H., Davis, B.A., Boulton, A.A., Aliphatic propargylamines as specific MAO-B inhibitors and as neuroprotective agents. United States Patent No. 5,508,311 (1992).

16. Durden, D.A., et al., Aliphatic propargylamines as cellular rescue agents. United States Patent No. 5,840,979 (1997).

17. Grace, J.M., M.T. Kinter, and T.L. Macdonald, Atypical metabolism of deprenyl and its enantiomer, (S)-(+)-N,alpha-dimethyl-N-propynylphenylethylamine, by cytochrome P450 2D6. Chem. Res. Toxicol., 1994. **7**: p. 286-290.

18. Komives, E.A. and P.R. Ortiz de Montellano, Mechanism of oxidation of π bonds by cytochrome P-450. J. Biol. Chem., 1987. **262**: p. 9793-9802.

19. Roberts, E.S., et al., Mechanism-based inactivation of cytochrome 450 2B1 by 9-ethynylphenanthrene. Arch. Biochem. Biophys., 1995. **323**: p. 295-302.

20. Valoti, M., et al., Interactions between substituted tryptamine analogues, MAO inhibitors and cytochrome P-450. J. Neural Transm. [Suppl], 1994. **41**: p. 291-293.

21. Tarbell, D.S., et al., The synthesis of some 7-chloro-4-(3-alkylaminopropylamino)quinolines. J. Am. Chem. Soc., 1946. **68**: p. 1217-1219.

22. Mazur, R.H., Absolute configuration of 1-methylalkylamines. J. Organic Chemistry, 1970. **35**: p. 2050-2051.

23. Durden, D.A., B.A. Davis, and A.A. Boulton, Enantioselective gas chromatographic assay of 2-alkylamines using

N-(trifluoroacetyl)propyl derivatives and a chiral capillary column. Journal of Chromatography B, 1997. **689**: p. 165-173.

24. Robinson, J.B. and J. Thomas, The preparation of N-t-butyl-4-piperidone. J. Chem. Soc., 1965: p. 2270-2271.

25. Arnold, C. and D.N. Thatcher, Preparation and reactions of 5-vinyltetrazole. J. Org. Chem., 1969. **34**: p. 1141-1142.

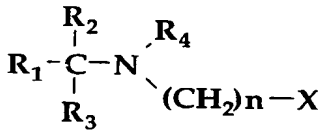
26. Loibner, H., A. Pruckner, and A. Stutz, Reductive methylation of amines. Tetrahedron Lett., 1984. **25**: p. 2535-2536.

27. Dessi, F., et al., Cytosine arabinoside induces apoptosis in cerebellar neurons in culture. J. Neurochem., 1995. **64**: p. 1980-1987.

28. Enokido, Y., et al., P53 involves cytosine arabinoside induced apoptosis in cultured cerebellar granule neurons. Neurosci. Lett., 1996. **203**: p. 1-4.

WE CLAIM:

1. A compound of the Formula I



Formula I

wherein:

R_1 is $(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms,

R_2 = H, CH_3 or CH_2CH_3,

R_3 = H or CH_3,

R_4 = H or CH_3,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH) or carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula I according to claim 1 wherein:

R_1 = $(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16,

R_2 = CH_3,

R_3 = H,

R_4 = H or CH_3,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH) or carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

3. A compound of the Formula I according to claim 1 wherein:
$R_1 = (CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16,
$R_2 = CH_3$,
$R_3 = H$,
$R_4 = H$ or CH_3,
R_5 = lower alkyl having from 1 to 5 carbon atoms,
n is an integer in the range from 1 to 3,
and X is carboxyl (COOH) or carbalkoxy ($COOR_5$) cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, as a substantially pure enantiomer in the R-configuration, or a pharmaceutically acceptable salt thereof.

4. A compound of the formula I according to claim 1 wherein:
$R_1 = (CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16,
$R_2 = CH_3$,
$R_3 = H$,
$R_4 = H$ or CH_3,
R_5 = lower alkyl having from 1 to 5 carbon atoms,
n is an integer in the range from 1 to 3,
and X is carboxyl (COOH) or carbalkoxy ($COOR_5$) cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, as a substantially pure enantiomer in the S-configuration, or a pharmaceutically acceptable salt thereof.

5. A compound of the Formula I according to claim 1 wherein:
$R_1 = (CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16,

$R_2 = CH_3$,

$R_3 = H$,

$R_4 = H$ or CH_3,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH) or carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, wherein the compound is racemic or achiral and with the following exclusions:

a) for X = COOH; n = 1; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = H$ and m = 1 to 4, 6, 7, 9, 11, or 13, and

$R_2 = CH_3$ and m= 0, 1 or 2;

b) for X= COOH; n = 1; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:

$R_2 = H$ and m = 2 or 3, and

$R_2 = CH_3$ and m = 0;

c) for X = $COOR_5$; n = 1; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = H$ and m = 1 to 4, or 9, and

$R_2 = CH_3$ and m = 0 or 1, and

R_5 = methyl, ethyl, t-butyl;

d) for X = COOH; n = 2; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = H$ and m = 1 to 4, 6, 9 or 11, and

$R_2 = CH_3$ and m = 0, 1 or 4;

e) for X = COOH; n = 2; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:

$R_2 = H$ and m = 1 or 2;

f) for X = $COOR_5$; n = 2; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = H$ and m = 1 to 5, 9 or 15,

$R_2 = CH_3$ and m = 0 or 1, and

R_5 = methyl, ethyl, t-butyl;

g) for X = $COOR_5$; n = 2; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:

$R_2 = H$ and m = 1 or 2,

$R_2 = CH_3$ and m = 0, and

R_5 = methyl, ethyl, t-butyl;

h) for X = COOH; n = 3; R_3 = R_4 = H, exclude compounds for which:

R_2 = H and m = 2 or 6;

i) for X = $COOR_5$; n= 3; R_3 = R_4 = H, exclude compounds for which:

R_2 = H and m = 2,

R_2 = CH_3 and m = 0 or 1, and

R_5 = methyl, ethyl, t-butyl;

j) for X = C≡N (cyano); n = 1; R_3 = R_4 = H, exclude compounds for which:

R_2 = H and m = 1, 2, 4, 5 or 6, and

R_2 = CH_3 and m = 0, 1 or 2;

k) for X = C≡N; n = 1; R_3 = H; R_4 = CH_3, exclude compounds for which:

R_2 = H and m = 1, and

R_2 = CH_3 and m = 0;

l) for X = C≡N; n = 2; R_3 = R_4 = H, exclude compounds for which:

R_2 = H and m = 1, 2, 3, 4 or 6, and

R_2 = CH_3 and m = 0, 1 or 4;

m) for X = C≡N; n = 2; R_3 = H; R_4 = CH_3, exclude compounds for which:

R_2 = H and m = 2, and

R_2 = CH_3 and m = 0;

n) for X = C≡N; n = 3; R_3 = R_4 = H, exclude compounds for which:

R_2 = H and m = 1 to 4, and

R_2 = CH_3 and m = 1 or 2;

o) for X = PO_3H_2; n = 2; R_3 = R_4 = H, exclude compounds for which:

R_2 = CH_3 and m = 0, 1 or 5;

p) for X = $PO_3(R_5)_2$; n = 2; R_3 = R_4 = H, exclude compounds for which:

R_2 = CH_3 and m = 0 or 1, and

R_5 = ethyl; and

q) for X = 5-tetrazole; n = 2; R_3 = R_4 = H, exclude compounds for which:

$R_2 = CH_3$ and m = 0.

6. A compound of the Formula I according to any one of claims 1 to 5 wherein R_1 is substituted with at least one of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3 and 6 atoms, of which from 1 to 3 are heteroatoms selected from O, S and/or N.

7. A compound according to claim 3, wherein said compound of formula I is selected from the group consisting of:
(R)-3-(2-Heptylamino)propionic acid;
(R)-3-(2-Heptylmethylamino)propionic acid;
Methyl (R)-3-(2-heptylamino)propionate;
Methyl (R)-3-(2-heptylmethylamino)propionate;
(R)-2-(2-Pentylamino)acetonitrile;
(R)-2-(2-Pentylmethylamino)acetonitrile;
(R)-3-(2-Heptylamino)propionitrile;
(R)-3-(2-Heptylmethylamino)propionitrile;
(R)-2-(2-Pentylamino)ethanephosphonic acid;
(R)-2-(2-Pentylmethylamino)ethanephosphonic acid; and
(R)-2-(2-Heptylamino)ethane-5-tetrazole.

8. A compound according to claim 4, wherein said compound of formula I is selected from the group consisting of:
(S)-2-(2-Heptylamino)acetic acid;
(S)-2-(2-Heptylmethylamino)acetic acid;
Methyl (S)-2-(2-heptylamino)acetate;
Methyl (S)-2-(2-heptylmethylamino)acetate;
(S)-2-(2-Heptylamino)acetonitrile;
(S)-2-(2-Heptylmethylamino)acetonitrile;

(S)-2-(2-Heptylamino)ethanephosphonic acid; and
(S)-2-(2-Heptylmethylamino)ethanephosphonic acid.

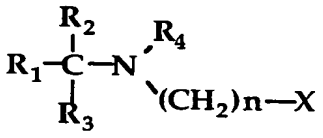
9. A compound according to claim 5, wherein said compound of formula I is selected from the group consisting of:
2-(1-Hexylmethylamino)acetic acid;
3-(2-Propylmethylamino)propionic acid;
Methyl 2-(2-propylmethylamino)acetate;
Methyl 2-(1-hexylmethylamino)acetate;
Methyl 3-(1-hexylmethylamino)propionate;
2-(1-Hexylamino)acetonitrile;
2-(1-Hexylmethylamino)acetonitrile;
3-(3-Pentylamino)propionitrile;
3-(3-Pentylmethylamino)propionitrile;
2-(2-Propylamino)ethanephosphonic acid; and
2-(2-Propylmethylamino)ethanephosphonic acid.

10. A compound according to any one of claims 1 to 9 in the form of a hydrochloride salt.

11. A compound according to any one of claims 3 to 9 wherein m is an integer from 1 to 12.

12. A compound according to any one of claims 3 to 9 wherein m is an integer from 1 to 9.

13. A composition for the treatment or prevention of a disease in which cell death occurs by apoptosis, which composition comprises an effective amount of a compound having the formula I:



Formula I

wherein:

R_1 is $(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms,

R_2 = H, CH_3 or CH_2CH_3,

R_3 = H or CH_3,

R_4 = H or CH_3

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof, in admixture with a suitable diluent or carrier.

14. A composition according to claim 13, wherein:

R_1 is $(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16,

R_2 = CH_3,

R_3 = H,

R_4 = H or CH_3,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof, in admixture with a suitable diluent or carrier.

15. A composition according to claim 13 or 14, wherein R_1 differs from R_2, R_3 = H and the compound is in the R-configuration.

16. A composition according to claim 13 or 14, wherein R_1 differs from R_2, R_3 = H and the compound is in the S-configuration.

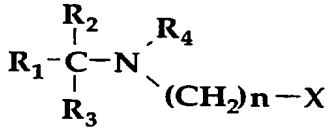
17. A composition according to any one of claims 13 to 16, wherein R_1 is substituted with at least one of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3 and 6 atoms, of which from 1 to 3 are heteroatoms selected from O, S and/or N.

18. A composition according to claim 13 or 14, wherein said compound of formula I is selected from the group consisting of:
2-(2-Propylamino)acetic acid;
2-(1-Hexylamino)acetic acid;
(S)-2-(2-Heptylamino)acetic acid;
3-(2-Propylamino)propionic acid;
3-(1-Hexylamino)propionic acid;
(R)-3-(2-Heptylamino)propionic acid;
2-(2-Propylmethylamino)acetic acid;
2-(1-Hexylmethylamino)acetic acid;
(S)-2-(2-Heptylmethylamino)acetic acid;
3-(2-Propylmethylamino)propionic acid;
3-(1-Hexylmethylamino)propionic acid;
(R)-3-(2-Heptylmethylamino)propionic acid;
2-(2-Propylamino)acetonitrile;
(R)-2-(2-Pentylamino)acetonitrile;
2-(1-Hexylamino)acetonitrile;
(S)-2-(2-Heptylamino)acetonitrile;

(R)-3-(2-Heptylamino)propionitrile;
2-(2-Propylmethylamino)acetonitrile;
(R)-2-(2-Pentylmethylamino)acetonitrile;
2-(1-Hexylmethylamino)acetonitrile;
(S)-2-(2-Heptylmethylamino)acetonitrile;
(R)-3-(2-Heptylmethylamino)propionitrile;
2-(2-Propylamino)ethanephosphonic acid;
(R)-2-(2-Pentylamino)ethanephosphonic acid;
(S)-2-(2-Heptylamino)ethanephosphonic acid;
2-(2-Propylmethylamino)ethanephosphonic acid;
(S)-2-(2-Heptylmethylamino)ethanephosphonic acid; and
(R)-2-(2-Heptylamino)ethane-5-tetrazole.

19. A composition according to claim 18, wherein the compound of formula I is in the form of a hydrochloride salt.

20. A use of a compound of the formula I for the treatment or prevention of a disease in which cell death occurs by apoptosis, wherein said compound has the formula I:



Formula I

wherein:

R_1 is $(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms,

R_2 = H, CH_3 or CH_2CH_3

R_3 = H or CH_3

R_4 = H or CH_3

R_5 = lower alkyl having 1 to 5 carbon atoms

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

21. A use according to claim 20, wherein

R_1 is $(CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16,

$R_2 = CH_3$,

$R_3 = H$,

$R_4 = H$ or CH_3,

R_5 = lower alkyl having 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy ($COOR_5$), cyano (C≡N), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

22. A use according to claim 20 or 21 wherein R_1 is substituted with at least one of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3 and 6 atoms, of which from 1 to 3 are heteroatoms selected from O, S and/or N.

23. A use according to claim 20 wherein said compound of Formula I is selected from the group consisting of:

2-(2-Propylamino)acetic acid;

2-(1-Hexylamino)acetic acid;

(S)-2-(2-Heptylamino)acetic acid;

3-(2-Propylamino)propionic acid;

3-(1-Hexylamino)propionic acid;

(R)-3-(2-Heptylamino)propionic acid;

2-(2-Propylmethylamino)acetic acid;
2-(1-Hexylmethylamino)acetic acid;
(S)-2-(2-Heptylmethylamino)acetic acid;
3-(2-Propylmethylamino)propionic acid;
3-(1-Hexylmethylamino)propionic acid;
(R)-3-(2-Heptylmethylamino)propionic acid;
2-(2-Propylamino)acetonitrile;
(R)-2-(2-Pentylamino)acetonitrile;
2-(1-Hexylamino)acetonitrile;
(S)-2-(2-Heptylamino)acetonitrile;
(R)-3-(2-Heptylamino)propionitrile;
2-(2-Propylmethylamino)acetonitrile;
(R)-2-(2-Pentylmethylamino)acetonitrile;
2-(1-Hexylmethylamino)acetonitrile;
(S)-2-(2-Heptylmethylamino)acetonitrile;
(R)-3-(2-Heptylmethylamino)propionitrile;
2-(2-Propylamino)ethanephosphonic acid;
(R)-2-(2-Pentylamino)ethanephosphonic acid;
(S)-2-(2-Heptylamino)ethanephosphonic acid;
2-(2-Propylmethylamino)ethanephosphonic acid;
(S)-2-(2-Heptylmethylamino)ethanephosphonic acid; and
(R)-2-(2-Heptylamino)ethane-5-tetrazole.

24. A use according to any one of claims 20 to 23 wherein the disease is selected from the group consisting of stroke, head trauma, Bell's palsy, spinal cord injury, Alzheimer's disease, Parkinson's disease, Pick's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, cardiac myopathies, nephropathy, retinopathy, diabetic complications, glaucoma and idiopathic neuropathies.

25. A use according to any one of claims 20 to 24, for the treatment of a human.

26. A commercial package for the treatment or prevention of a disease in which cell death occurs by apoptosis, said package comprising a pharmaceutical composition according to any one of claims 13 to 19, together with instructions for use in the treatment or prevention of diseases in which cell death occurs by apoptosis.